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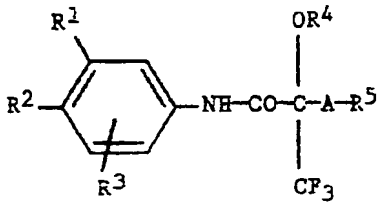
Description

This invention relates to new acylanilide derivatives which possess progestational activity.

Many acylanilides chemically-related to those hereinafter described are known to possess antiandrogenic activity. Of these, flutamide and hydroxyflutamide have been known for some considerable time, and others are described in Applicant's European Specifications Nos, 2309, 2892, 40932, 79191 and 100172.

We have now discovered that a small group of acylanilides surprisingly possess no anitandrogenic activity, but potent progestational activity.

According to the invention there is provided an acylanilide of the formula:



wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein R^3 is hydrogen or halogen;
wherein R^4 is hydrogen or acyl of up to 15 carbon atoms;
wherein A is branched-chain alkylene of up to 6 carbon atoms;
and wherein R^5 is phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, hydroxy, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and N-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R^5 is naphthyl.

It will be observed that the acylanilide derivative of the invention possesses an asymmetric carbon atom, namely the carbon atom which bears the substituent OR^4, and it can therefore exist in racemic and optically-active forms. Furthermore, frequently the branched-chain alkylene group -A-will also possess an asymmetric carbon atom in which case pairs of diastereoisomers, in optically-active or racemic form, are also possible. It is to be understood that this invention encompasses any racemic form of the acylanilide derivative and any optically-active form which possesses progestational activity, it being a matter of common general knowledge how a racemic compound may be resolved into its optically-active forms and how any progestational activity present in any of these forms may be determined.

A suitable value for R^1 when it is alkyl, or for an alkyl substituent in R^5 when R^5 is phenyl substituted by alkyl is, for example, methyl or ethyl.

A suitable value for R^1 when it is alkoxy, or for an alkoxy substituent in R^5 when R^5 is phenyl substituted by alkoxy is, for example, methoxy or ethoxy.

A suitable value for R^1 or R^2 when it is alkanoyl, or for an alkanoyl substituent in R^5 when R^5 is phenyl substituted by alkanoyl is, for example, formyl or acetyl.

A suitable value for R^1 or R^2 when it is alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl, or for such a substituent in R^5 when R^5 is phenyl bearing such a substituent is, for example, methylthio, ethylthio, methylsulphinyl, methylsulphonyl, trifluoromethyl, pentafluoroethyl, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl.

A suitable value for R^3 when it is halogen, or for a halogen substituent in R^5 when R^5 is phenyl substituted by halogen, is fluoro, chloro, bromo or iodo.

R^3 is preferably hydrogen or chloro, especially hydrogen.

A suitable value for an alkoxycarbonyl or N-alkylcarbamoyl substituent in R^5 when R^5 is phenyl bearing

such a substituent is, for example, methoxycarbonyl, ethoxycarbonyl or N -methylcarbamoyl.

A suitable value for R^4 when it is acyl is, for example, alkanoyl or aroyl each of up to 15 carbon atoms, for example acetyl, propionyl, decanoyl, dodecanoyl or benzoyl.

R^4 is preferably hydrogen, A suitable value for A is, for example, 2-methylethylene or 2,2-dimethylethylene.

A preferred combination of values for R^1 and R^2 is as follows:-

R^1	R^2
trifluoromethyl	nitro
trifluoromethyl	cyano
chloro	chloro
chloro	nitro
chloro	cyano
cyano	cyano
nitro	cyano
ethoxy	nitro
chloro	methylsulphonyl

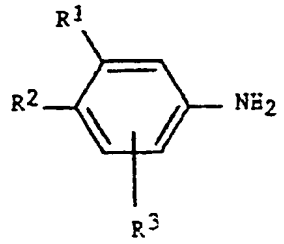
A preferred acylanilide of the invention has the formula stated above wherein R^1 and R^2, which may be the same or different, each is cyano, nitro, trifluoromethyl, methylthio, methylsulphinyl, methylsulphonyl or chloro, R^3 and R^4 are both hydrogen, A is 2-methylethylene or 2,2-dimethylethylene and R^5 is phenyl which is unsubstituted or which bears one fluoro, chloro, hydroxy, methyl, nitro, methylthio, methylsulphinyl or methylsulphonyl substituent.

Specific acylanilides of the invention are hereinafter described in the Examples.

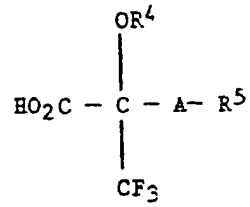
A particularly active compound is N (2-hydroxy-4-phenyl-2-trifluoromethylpentanoyl)-4-nitro-3-trifluoromethylaniline in either of its diastereoisomeric forms.

The acylanilides of the invention may be manufactured by any chemical process known to be suitable for the manufacture of chemically-analogous compounds.

A preferred process for the manufacture of an acylanilide of the invention comprises the reaction of an amine of the formula:-



wherein R^1, R^2 and R^3 have the meanings stated above, with an acid of the formula:-



wherein R^4, R^5 and A have the meanings stated above, or with a reactive derivative of said acid.

A suitable reactive derivative of an acid is, for example, an acid anhydride, or an acyl halide, for example an acyl chloride, or a lower alkyl ester of said acid, for example the methyl or ethyl ester.

Preferably the reaction is carried out in N , N -dimethylacetamide solution using an acyl chloride (prepared from the acid and thionyl chloride) as reactant.

An acylanilide of the invention wherein R^4 is hydrogen may be prepared by the hydrolysis of the corresponding acylanilide wherein R^4 is acyl, and conversely, an acylanilide of the invention wherein R^4 is acyl may be prepared by the acylation of the corresponding acylanilide wherein R^4 is hydrogen.

An acylanilide of the invention wherein one or more of R^1, R^2 and a substituent in the phenyl group R^5 is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, may be prepared by the oxidation of the corresponding acylanilide wherein one or more of R^1, R^2 and a substituent in the phenyl group R^5 is alkylthio, perfluoroalkylthio or phenylthio, respectively. The oxidising agent and conditions used will determine whether a sulphinyl or a sulphonyl compound is obtained. Thus, oxidation with sodium metaperiodate in methanol solution at or below laboratory temperature will generally convert a thio compound into the corresponding sulphinyl compound; and oxidation with a peracid, for example m -chloroperbenzoic acid in methylene chloride solution at or above laboratory temperature will generally convert a thio compound into the corresponding sulphonyl compound.

A racemic acylanilide of the invention wherein R^4 is hydrogen may be separated into its optical isomers by forming an ester of the hydroxy group OR^4 with an optically-active acid, for example (-)-camphanic acid, separating the diastereoisomeric esters thus obtained, by fractional crystallisation or, preferably, by flash-chromatography, and then hydrolysis of each separate ester to the alcohol.

As stated above, an acylanilide of the invention possesses progestational properties as demonstrated by its ability to promote glandular development in the endometrium of an oestrogen-primed immature rabbit, the standard Clauberg assay procedure. An acylanilide of the invention may therefore be used as an oral contraceptive, and in the treatment of menstrual disorders, such as dysmenorrhea, dysfunctional bleeding and premenstrual tension, and in the treatment of hormone dependent tumors, especially those of the breast or endometrium. It may also be used for the synchronisation of oestrus and for the maintainence of early pregnancy in domestic animals such as cattle. At a dose of an acylanilide of the invention which produces progestational activity in rabbits no symptoms of toxicity are apparent.

The acylanilide of the invention may be adminstered to a warm blood animal in the form of a pharmaceutical or veterinary composition which comprises the acylanilide in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion. It may alternatively be in the form of a sterile solution or suspension suitable for patenteral administration, or be in the form of an ointment or lotion for topical administration or be in the form of a suppository for anal or vaginal administration.

The composition may additionally contain one or more drugs selected from oestrogens, for example, ethynyloestradiol or mestranol (which combination may be used as an oral contraceptive); antioestrogens, for example tamoxifen; androgens, for example cyproterone acetate and methyltestosterone; and gonadotrophin releasing factors and analogues thereof and antagonists thereof.

The acylanilide of the invention will normally be administered to a warm-blooded animal at a dose of between 0.1 mg. and 125 mg. per kg. bodyweight.

The invention is illustrated but not limited by the following Examples:-

Example 1

Thionyl chloride (0.82 ml.) was added dropwise to a stirred solution of 2-hydroxy-4-phenyl-2-

trifluoromethylpentanoic acid (isomer A, m.p. 145-146°C.) in dimethylacetamide (60 ml.) which was maintained at -15°C. under an atmosphere of argon, the mixture was stirred at that temperature for 1 hour and 4-nitro-3-trifluoromethylaniline (1.9 g.) was added. The mixture was stirred at -15°C. for 1 hour and then at laboratory temperature for 20 hours, and was then poured into water (700 ml.). The mixture was extracted six times with diethyl ether (100 ml.) each time) and the combined extracts were washed twice with aqueous 10% w/v sodium carbonate solution (50 ml. each time), dried over magnesium sulphate and evaporated to dryness. The residue was purified by flash chromatography on a silica gel column (Merck 9835) using a 2:1 v/v mixture of petroleum ether (b.p. 60-80°C.) and ethyl acetate as eluant. There was thus obtained N -(2-hydroxy-4-phenyl-2-trifluoromethylpentanoyl)-4-nitro-3-trifluoromethylaniline, m.p. 162-163°C. (more polar isomer).

The pentanoic acid used as starting material was obtained as follows:-

1,1,1-Trifluoromethyl-4-phenylpentan-2-one (116.7 g.; b.p. 82-83°C./10 mm. Hg.; prepared by the general process described in the Journal of Organic Chemistry, 1967, 32 , 1316) was added dropwise to a cooled stirred solution of potassium cyanide (37.85 g.) in water (240 ml.) at such a rate that the temperature of the mixture was maintained at between 0°C. and 5°C. A 4:1 v/v mixture of water and concentrated sulphuric acid (300 ml.) was added at such a rate as to maintain the above temperature, and the mixture was stirred at laboratory temperature for 15 hours and then extracted four times with diethyl ether (90 ml. each time). The combined extracts were washed three times with water (100 ml. each time), dried over magnesium sulphate and evaporated to dryness under reduced pressure.

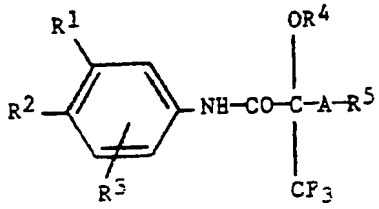
A mixture of the cyanhydrin thus obtained as a mixture of diastereoisomers (6.0 g.), concentrated aqueous hydrochloric acid (45 ml.) and glacial acetic acid (15 ml.) was vigorously stirred and heated at 100°C. for 48 hours, cooled and poured onto ice (125 g.). The mixture was extracted three times with diethyl ether (50 ml. each time) and the combined extracts were washed with water (50 ml.) and then extracted three times with saturated aqueous sodium carbonate solution (50 ml. each time). The combined extracts were acidified with concentrated aqueous hydrochloric acid and extracted three times with diethyl ether (50 ml. each time). The combined extracts were washed with water (50 ml.) and saturated aqueous sodium chloride solution (50 ml.), dried over magnesium sulphate and evaporated to dryness. The residue was stirred with petroleum ether (b.p. 60-80°C.) and the mixture was filtered. There was thus obtained as solid residue isomer A of 2-hydroxy-4-phenyl-2-trifluoromethylpentanoic acid, m.p. 145-146°C. The petroleum ether filtrate was evaporated to dryness and there was thus obtained as residue a solid, m.p. 101-102°C., which was predominantly isomer B of 2-hydroxy-4-phenyl-2-trifluoromethylpentanoic acid contaminated with a small amount of isomer A.

Example 2

The process described in Example 1 was repeated using the impure isomer B of the pentanoic acid (m.p. 101-102°C.) as starting material in place of isomer A. The product was purified by flash chromatography on silica gel (Merck 9385) using a 3:2 v/v mixture of petroleum ether (b.p. 60-80°C.) and ethyl acetate as eluant, and the product obtained was crystallised from a 2:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60-80°C.). There was thus obtained N -(2-hydroxy-4-phenyl-2-trifluoromethylpentanoyl)-4-nitro-3-trifluoromethylaniline, m.p. 145-146°C. (less polar isomer).

Claims

1. An acylanilide of the formula:

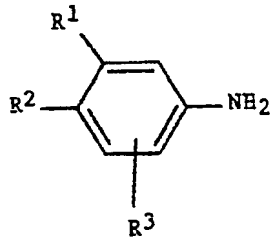


wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein R^3 is hydrogen or halogen;
wherein R^4 is hydrogen or acyl of up to 15 carbon atoms;
wherein A is branched-chain alkylene of up to 6 carbon atoms;
and wherein R^5 is phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, hydroxy, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and N -alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R^5 is naphthyl.

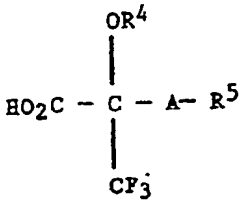
2. An acylanilide as claimed in claim 1, wherein R^1 and R^2, which may be the same or different, each is cyano, nitro, trifluoromethyl, methylthio, methylsulphinyl, methylsulphonyl or chloro, R^3 and R^4 are both hydrogen, A is 2-methylethylene or 2,2-dimethylethylene and R^5 is phenyl which is unsubstituted or which bears one fluoro, chloro, hydroxy, methyl, nitro, methylthio, methylsulphinyl methylsulphonyl substituent.

3. The compound N -(2-hydroxy-4-phenyl-2-trifluoromethylpentanoyl)-4-nitro-3-trifluoromethylaniline in either of its diastereoisomeric forms.

4. A process for the manufacture of an acylanilide claimed in claim 1 which comprises:-
(a) the reaction of an amine of the formula:-



wherein R^1, R^2 and R^3 have the meanings stated in claim 1 with an acid of the formula:-



wherein R^4, R^5 and A have the meanings stated in claim 1 or with a reactive derivative of said acid;
(b) for the manufacture of an acylanilide of the invention wherein R^4 is hydrogen, the hydrolysis of the corresponding anylanilide wherein R^4 is acyl;
(c) for the manufacture of an acylanilide of the invention wherein R^4 is acyl, the acylation of the corresponding acylanilide wherein R^4 is hydrogen;
(d) for manufacture of an acylanilide of the invention wherein one or more of R^1, R^2 and a substituent in the phenyl group R^5 is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, the oxidation of the corresponding acylanilide wherein one or more of R^1, R^2 and a substituent in the phenyl group R^5 is alkylthio, perfluoroalkylthio or phenylthio, respectively or
(e) for the separation into its optical isomers of an acylanilide of the invention wherein R^4 is hydrogen, the formation of an ester of the hydroxy group OR^4 with an optically-active acid, the separation of the diastereoisomeric esters thus obtained by fractional crystallisation or by flash-chromatography, and then the hydrolysis of each separate ester to the alcohol.

5. A pharmaceutical or veterinary composition comprising an acylanilide as claimed in claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

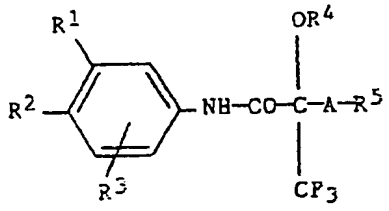
6. A composition as claimed in claim 5 which is in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion; or in the form of a sterile solution or suspension suitable for parenteral administration, or in the form of an ointment or lotion for topical administration or in the form of a suppository for anal or vaginal administration.

7. A composition as claimed in claim 5 which additionally contains one or more drugs selected from oestrogens, antioestrogens, androgens and gonadotrophin releasing factors and analogues thereof and antagonists thereof.

8. The use of an acylanilide as claimed in claim 1 for the manufacture of a medicament for producing a progestational effect in a warm-blooded animal.

Revendications

1. Acylanilide de fomule :



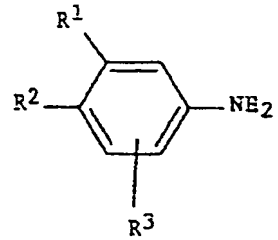
dans laquelle R^1 représente un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo, iodo ou

l'hydrogène, ou un groupe alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle, chacun de ces groupes ayant jusqu'à 4 atomes de carbone, ou un groupe phénylthio, phénylsulfinyle ou phénylsulfonyle ; R^2 représente un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo ou iodo, ou un groupe alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle, chacun de ces groupes ayant jusqu'à 4 atomes de carbone, ou un groupe phénylthio, phénylsulfinyle ou phénylsulfonyle ; R^3 représente l'hydrogène ou un halogène ; R^4 représente l'hydrogène ou un groupe acyle ayant jusqu'à 15 atomes de carbone ; A représente un groupe alkylène à chaîne ramifiée ayant jusqu'à 6 atomes de carbone ; et R^5 représente un groupe phényle qui porte un, deux ou trois substituants choisis entre l'hydrogène, un halogène, des groupes nitro, hydroxy, carboxy, carbamoyle et cyano, et des groupes alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle, perfluoralkylsulfonyle, alkoxycarbonyle et N -alkylcarbamoyle, chacun de ces groupes ayant jusqu'à 4 atomes de carbone ; et des groupes phényle, phénylthio, phénylsulfinyle et phénylsulfonyle ; ou bien R^5 représente un groupe naphtyle.

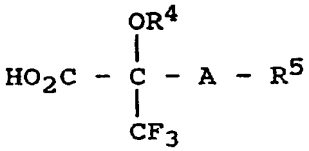
2. Acylanilide suivant la revendication 1, dans lequel R^1 et R^2, qui peuvent être identiques ou différents, représentent chacun un groupe cyano, nitro, trifluorométhyle, méthylthio, méthylsulfinyle, méthylsulfonyle ou chloro, R^3 et R^4 représentent l'un et l'autre l'hydrogène, A représente un groupe 2-méthyléthylène ou 2,2-diméthyléthylène et R^5 représente un groupe phényle qui est non substitué ou qui porte un substituant fluoro, chloro, hydroxy, méthyle, nitro, méthylthio, méthylsulfinyle ou méthylsulfonyle.

3. N -(2-hydroxy-4-phényl-2-trifluorométhylpentanoyl)-4-nitro-3-trifluorométhylaniline, sous chacune de ses formes diastéréo-isomères.

4. Procédé de production d'un acylanilide suivant la revendication 1, qui consiste :
(a) à faire réagir une amine de formule :



dans laquelle R^1, R^2 et R^3 répondent aux définitions suivant la revendication 1, avec un acide de formule :



dans laquelle R^4, R^5 et A répondent aux définitions suivant la revendication 1, ou avec un dérivé réactif de cet acide ;
(b) pour la production d'un acylanilide conforme à la présente invention, dans lequel R^4 représente l'hydrogène, à hydrolyser l'acylanilide correspondant dans lequel R^4 représente un groupe acyle ;
(c) pour la production d'un acylanilide conforme à la présente invention, dans lequel R^4 représente un groupe acide, à acyler l'acylanilide correspondant dans lequel R^4 représente 1'hydrogène ;
(d) pour la production d'un acylanilide conforme à la présente invention, dans lequel un ou plusieurs groupes R^1, R^2 et un substituant dans le groupe phényle R^5 représentent des groupes alkylsulfinyle,

perfluoralkylsulfinyle ou phénylsulfinyle, ou bien représentent des groupes alkylsulfonyle, perfluoralkylsulfonyle ou phénylsulfonyle, à oxyder l'acylanilide correspondant dans lequel un ou plusieurs groupes R^1, R^2 et un substituant dans le groupe phényle R^5 représentent respectivement des groupes alkylthio, perfluoralkylthio ou phénylthio, ou

(e) pour la séparation en ses isomères optiques d'un acylanilide conforme à la présente invention, dans lequel R^4 représente l'hydrogène, à former un ester du groupe hydroxy OR^4 avec un acide optiquement actif, à séparer les esters diastéréo-isomères ainsi obtenus par cristallisation fractionnée ou par chromatographie instantanée, puis à hydrolyser chaque ester séparé en l'alcool.

5. Composition pharmaceutique ou vétérinaire comprenant un acylanilide suivant la revendication 1, en association avec un diluant ou support pharmaceutiquement acceptable.

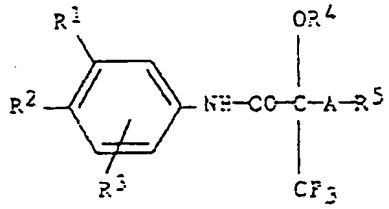
6. Composition suivant la revendication 5, qui est sous une forme convenable pour l'administration par voie orale, telle qu'un comprimé, une capsule, une solution, suspension ou émulsion aqueuse ou huileuse ; ou sous forme d'une solution ou suspension stérile convenable pour l'administration parentérale, ou sous forme d'une pommade ou d'une lotion pour l'administration topique, ou sous forme d'un suppositoire pour l'administration anale ou vaginale.

7. Composition suivant la revendication 5, qui contient en outre un ou plusieurs médicaments choisis entre des oestrogènes, des anti-oestrogènes, des androgènes et des facteurs de libération de gonadotrophine, ainsi que leurs analogues et antagonistes.

8. Utilisation d'un acylanilide suivant la revendication 1, pour la production d'un médicament destiné à engendrer un effet progestatif chez un animal à sang chaud.

Ansprüche

1. Acylanilid der Formel



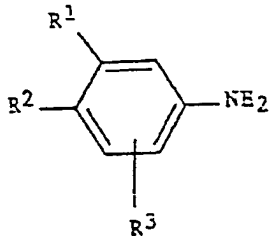
worin R^1 für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo, Jodo oder Wasserstoff oder für Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder für Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht; R^2 für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo oder Jodo oder für Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl , Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder für Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht; R^3 für Wasserstoff oder Halogen steht; R^4 für Wasserstoff oder Acyl mit bis zu 15 Kohlenstoffatomen steht; A für verzweigtes Alkylen mit bis zu 6 Kohlenstoffatomen steht; und R^5 für Phenyl, das einen, zwei oder drei Substituenten trägt, die ausgewählt sind aus Wasserstoff, Halogen, Nitro, Hydroxy, Carboxy, Carbamoyl und Cyano, aus Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl, Perfluoroalkylsulfonyl, Alkoxycarbonyl und N-Alkylcarbamoyl mit jeweils bis zu 4 Kohlenstoffatomen und aus Phenyl, Phenylthio, Phenylsulfinyl und Phenylsulfonyl, oder für Naphthyl steht.

2. Acylanilid nach Anspruch 1, worin R^1 und R^2, welche gleich oder verschieden sein können, jeweils für Cyano, Nitro, Trifluoromethyl, Methylthio, Methylsulfinyl, Methylsulfonyl oder Chloro stehen, R^3 und R^4 beide für Wasserstoff stehen, A für 2-Methylethylen oder 2,2-Dimethylehtylen steht und R^5 für Phenyl

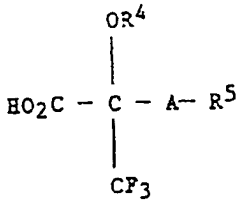
steht, das unsubstituiert ist oder das einen Fluoro-, Chloro-, Hydroxy-, Methyl-, Nitro-, Methylthio-, Methylsulfinyl- oder Methylsulfonyl-Substituenten trägt.

3. Die Verbindung N-(2-Hydroxy-4-phenyl-2-trifluoromethylpentanoyl)-4-nitro-3-trifluoromethylanilin in jeder ihrer diastereoisomeren Formen.

4. Verfahren zur Herstellung eines Acylanilids nach Anspruch 1, bei welchem (a) ein Amin der Formel



worin R^1 , R^2 und R^3 die in Anspruch 1 angegebenen Bedeutungen besitzen, mit einer Säure der Formel



worin R^4, R^5 und A die in Anspruch 1 angegebenen Bedeutungen besitzen, oder mit einem reaktiven Derivat dieser Säure umgesetzt wird; (b) zur Herstellung eines erfindungsgemäßen Acylanilids, worin R^4 für Wasserstoff steht, das entsprechende Acylanlid, worin R^4 für Acyl steht, hydrolysiert wird; (c) zur Herstellung eines erfindungsgemäßen Acylanilids, worin R^4 für Acyl steht, das entsprechende Acylanilid, worin R^4 für Wasserstoff steht, acyliert wird; (d) zur Herstellung eines erfindungsgemäßen Acylanilids, worin eines oder mehrere der Symbole R^1 und R^2 und ein Substituent in der Phenyl-Gruppe R^5 für Alkylsulfinyl, Perfluoroalkylsulfinyl oder Phenylsulfinyl oder für Alkylsulfonyl, Perfluoroalkylsulfonyl oder Phenylsulfonyl steht, das entsprechende Acylanilid, worin eines oder mehrere der Symbole R^1 und R^2 und ein Substituent in der Phenyl-Gruppe R^5 für Alkylthio, Perfluoroalkylthio, bzw. Phenylthio steht, oxidiert wird; oder (e) zur Trennung eines erfindungsgemäßen Acylanilids, worin R^4 für Wasserstoff steht, in seine optischen Isomere ein Ester der Hydroxy-Gruppe OR^4 mit einer optisch aktiven Säure hergestellt wird, der so erhaltene diastereomere Ester durch fraktionierte Kristallisation oder durch Entspannungschromatografie getrennt wird und jeder gesonderte Ester in den Alkohol hydrolysiert wird.

5. Pharmazeutische oder veterinäre Zusammensetzung, welche ein Acylanilid gemäß Anspruch 1 gemeinsam mit einem pharmazeutisch zulässigen Verdünnungs- oder Trägermittel enthält.

6. Zusammensetzung nach Anspruch 5, welche eine für orale Dosierung geeignete Form, wie z. B. die Form einer Tablette, Kapsel, wässerigen oder öligen Lösung oder Suspension oder Emulsion, oder die Form einer für parenterale Verabreichung geeigneten sterilen Lösung oder Suspension oder die Form einer für topische Verabreichung geeigneten Salbe oder Lotion oder die Form einer für anale oder vaginale Verabreichung geeigneten Suppositoriums aufweist.

7. Zusammensetzung nach Anspruch 5, welche zusätzlich ein oder mehrere Wirkstoffe enthält, die ausgewählt sind aus Östrogenen Antiöstrogenen, Androgenen und Gonadotrophinfreisetzungsfaktoren und Analogen davon und Antagonisten davon.

8. Die Verwenung eines Acylanilids nach Anspruch 1 für die Herstellung eines Medikamentes zur Erzeugung eines progestationalen Effekts bei Warmblütern.